ORIGINAL

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF TEXAS
DALLAS DIVISION

LASANDRA MADDEN Individually and on Behalf of LABREA WILLIAMS, a minor child,	§	
Plaintiffs,	§	
vs.	§	CIVIL ACTION NO. 3:03-CV-0167-BD
WYETH d/b/a WYETH, INC., f/k/a AMERICAN HOME PRODUCTS CORPORATION; WYETH CONSUMER HEALTHCARE, an unincorporated Division of WYETH, f/k/a WHITEHALL-ROBINS HEALTHCARE; AND WHITEHALL LABORATORIES, INC.,	§	
Defendants.	§	

PLAINTIFFS' RESPONSE TO DEFENDANT WYETH'S MOTION FOR SUMMARY JUDGMENT, WITH SUPPORTING BRIEF

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PLAINTIFFS' RESPONSE TO DEFENDANT WYETH'S MOTION FOR SUMMARY JUDGMENT

I. INDIVIDUAL CAUSATION ISSUE

A. Standard of review

The defendant is correct that the law requires that its conduct be a "substantial factor" in bringing about the plaintiff's harm, without which the harm would not have occurred. *See Havner v. EZ Mart Stores, Inc.*, 825 S.W.2d 456, 459 (Tex. 1992) (citation omitted). However, defendant has overlooked that proximate cause and producing cause are essentially fact questions and the Fifth Circuit has held that they should not be decided by summary judgment unless the stipulated facts conclusively establish as a matter of a law a defense barring recovery. *See, e.g.*, *Mauldin v. Upjohn Co.*, 697 F.2d 644, 647 (5th Cir. [La] 1983), *cert. denied*, 464 U.S. 848 (1983); *Anderson v. Sandoz Pharm. Corp.*, 77 F. Supp. 2d 804, 808–09 (S.D. Tex. 1999). In *Mauldin,* the drug manufacturer moved for summary judgment based on the testimony of the doctor, who said that he would have prescribed the drug anyway, regardless of the warning. *Mauldin*, 697 F.2d at 646. The Fifth Circuit held that this dispute presented a classic fact question for the jury, and a plaintiff's verdict was affirmed. *Id.* at 647.

Additionally, the "substantial factor" rule is usually invoked where there is evidence of two or more causes, which is not the case here, any one of which would have been sufficient to bring about the result. In such cases the "but for" rule is normally not determinative. *T&P Ry Co. v. McLeery*, 418 S.W.2d 494, 497 (Tex. 1967). And although the plaintiff does have the burden of proving causation in fact, this burden is met by a showing that the *greater probability* is that the occurrence was caused by the defendant's negligent act or omission. *See, e.g.*, *Farley*

v. M M Cattle Co., 529 S.W.2d 751, 755 (Tex. 1975). However, the plaintiff is *not* required to show that the occurrence could not possibly have been caused by any factor other than the defendant's act or omission, although plaintiffs have gone ahead and done so in the present case.

Additionally, defendant has overlooked that *something* caused this child's TEN and 70% of her skin to slough off, and caused her to almost die! The so-called "idiopathic" cases are 3% or less and all experts agree that: most TEN cases are caused by drugs; it is undisputed that ibuprofen can cause SJS and TEN; and the only suspect drug the child had taken in this case was ibuprofen! And none of the other known causes floated by the defendant have been or can be proven, such as infection or chemical or environmental causes. Therefore, defendant is relegated to reliance on the affidavit of one expert, Dr. Robert Stern, whose credibility is highly in issue, and nothing more.

Further, defendant's whole argument presupposes their right to judgment unless plaintiffs can prove that Children's Advil was the *sole cause* of this child's injuries; but this approach overlooks the fact that both the defense and plaintiffs' experts, as well as the literature, show that ibuprofen can have an *aggravating effect* on a pre-existing viral infection, thereby causing serious skin reactions including SJS and TEN, as will be shown.

Defendant's failure to warn and defective design may thereby be a *concurring cause* of plaintiffs' injuries, whether the initial symptoms were caused by the drug or not. *See, e.g.*, *Brownsville Med. Ctr. v. Gracia*, 704 S.W.2d 68, 73–74 (Tex. App.—Corpus Christi 1985, writ ref'd n.r.e.) (evidence sufficient to justify jury's conclusion that first hospital's negligence was concurring cause of child's death).

These negligence principles all apply equally to a products liability case, except that in a

products liability case the plaintiff must prove that the failure to warn (or defective design) was a "producing cause" of the plaintiff's condition or injury. *Technical Chem. Co. v. Jacobs*, 480 S.W.2d 602, 603 (Tex. 1972).

B. There is no credible evidence of any other probable cause other than ibuprofen.

The gist of defendant's factual and legal argument is contained in the following statement from its Brief: "Because the fever and blistering preceded the administration of the Children's Advil *and those are symptoms of SJS/TEN*, the Children's Advil could not have caused Labrea's illness as a matter of law." (***Def's. Brief***, p. 12) (emphasis added). However, its own expert, Dr. Jean-Claude Roujeau, admitted that "just because [she] had bumps and blisters on her face before she took the drug does not in and of itself conclusively prove they were symptoms of SJS." **(Att. 1—Roujeau dep.,** 165–66, *App.* 21–22). He also admitted the following:

> Q. (by Mr. Barber): Is there any clinical or laboratory evidence in the chart that the bumps and blisters that she exhibited when she woke up in the morning were caused by SJS or TEN?
>
> A. (by Dr. Roujeau): No. But there is something—***no, there is no good evidence.***

(Roujeau at 176:24–177:4, *App.* 24; *also id.* at 178:12–17, *App.* 25) (emphasis added).

Defendant's argument that plaintiffs cannot prove factual causation is based primarily on the Affidavit of Dr. Robert Stern, a Harvard dermatologist with close ties to the pharmaceutical industry, who has treated very few SJS and TEN patients compared to Dr. Roger Salisbury, plaintiffs' plastic and burn surgery expert. It is also important to note that *not one of this child's treating doctors support defendant's case here!* In fact, all of the treaters who have expressed

opinions have stated or suspected that ibuprofen was the cause.[1]

Stern admitted to treating fewer than 100 TEN patients over his career of approximately 35 years **(Att. 3—Stern dep.,** 76, 77, *App.* 59), compared to approximately 400 SJS and TEN patients treated by plaintiffs' expert Dr. Salisbury **(Att. 4—Aff. Roger Salisbury, M.D.,** p. 2, ¶2 *App.* 95), and only 5 to 25 pediatric TEN patients (Stern at 77, *App.* 59).[2] And he further admitted to never managing a TEN patient's care in a burn unit, even though he admitted that most serious TEN patients in the U.S. were treated in burn units. (*Id.* at 71–73, *App.* 58). Additionally, Stern admitted to earning approximately $600,000 in consulting fees from big pharma over the past twelve years. (*Id.* at 35–36, *App.* 56). His deposition was argumentative and most of his answers were unresponsive, and he repeatedly repudiated testimony he had given in a previous case, as well as his own statements in published articles.

Stern's argument is that since plaintiff Labrea Williams had symptoms that he believes to be symptoms of SJS and TEN prior to ingesting Children's Advil (active ingredient ibuprofen), it couldn't have been the drug that caused her SJS and TEN. This argument must be considered against the backdrop of undisputed medical evidence and literature showing that the overwhelming majority of TEN cases are caused by drugs; that ibuprofen is one of the drugs that

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[1] For example, Dr. Carter, the attending dermatologist at Parkland, recommended that ibuprofen be stopped because "since ibuprofen/NSAIDs are common causes of SJS/TEN, would avoid those meds if possible." **(Att. 2—Parkland Chart excerpts,** p. 140, *App.* 39). Dr. Purdue, her treating burn surgeon, stated at the end of her hospital stay that "7 y/o BF with Stevens-Johnson Synd after ingestion of Motrin [sic] (likely)." (***Id.*** at 2, *App.* 33). And throughout her chart, she was shown to be allergic to NSAIDs or ibuprofen. (*Cf.*, Parkland chart at 78, 189, 190, 191, 192, 193, *App.* 37, 44–48). Additionally, her treating pulmonologist in this case, Dr. Copenhaver, has filed an Affidavit in support of Plaintiffs' Motion for Partial Summary Judgment, stating his opinion that her TEN was caused by ibuprofen, as have her treating ophthalmologist, Dr. Tseng, and her treating neurologist, Dr. Walker. These Affidavits are incorporated by reference in this Response.

[2] It should also be pointed out that Stern's role in "treating" these patients is to make a diagnosis and determine the etiologic agent, and then pass the patient to a burn surgeon like plaintiffs' expert Dr. Salisbury or Dr. Purdue at Parkland to provide the ongoing care necessary to save their lives. (Stern at 75–77, *App.* 59).

has been proven to cause SJS and TEN; that there is no other suspect drug involved here; and by the further evidence in this case that there is no evidence of an infectious cause.

a. Defendant's experts agree that most TEN reactions are caused by drugs, including ibuprofen.

Both of defendant's causation experts, Stern and Roujeau, agree that the proper diagnosis in this case is Toxic Epidermal Necrolysis (TEN), even though Stern referred to it as consistent with "EM/ SJS/TEN" in his report. (Roujeau at 42, *App.* 4; Stern at 138–39, *App.* 67) Further, it is well settled in the medical literature that up to 95% of TEN cases are caused by drugs and the rest appear to be linked to infection or graft-versus-host disease, none of which are proven here. In a small percentage of patients with TEN (less than 5%), neither drugs nor other potential causes became apparent.[3]

Even defendant's causation experts have admitted that 80 to 85 (Stern) and 90 percent (Roujeau) of TEN reactions are caused by drugs. (Stern at 141, *App.* 67; Roujeau at 86–98, *App.* 8–11). Roujeau has written that as few as 3–4.5% of TEN cases are unrelated to drugs, citing two separate epidemiologic studies conducted in France. (Roujeau at 89, 92, 98, *App.* 8, 9, 11). This 3–4.5% is thought to be related to drugs that were unidentified by the patient or to unknown or idiopathic causes, as previously mentioned. (*Id.*). This is confirmed by plaintiffs' expert, Dr. Roger Salisbury. (Salisbury Aff. at 8, *App.* 101). In fact, defendant's expert Roujeau has written the following regarding so-called "idiopathic" cases:

> In fact, ***cases occurring without drug exposure have been so rare as to cast doubt on the reliability of the information about drug intake obtained from patients denying exposure.*** In our own series of 87 patients, only three patients

[3] Fitzpatrick, Dermatology in General Medicine, p.549 (6th ed. 2003). Fitzpatrick also lists vaccination as a possible cause, but this theory has been rejected by Dr. Roujeau. *See* Roujeau, Toxic Epidermal Necrolysis, *J Amer Acad Dermatol*, p.1046, *et seq.* (1990).

denied any drug intake before the onset of TEN.

Roujeau, *et al.*, Toxic epidermal necrolysis (Lyell syndrome), *J Amer Acad Dermatol*, Vol. 23, No. 6, Pt. 1, p. 1046 (Dec. 1990) (emphasis added).

b. Defendant and its experts agree that Children's Advil (ibuprofen) causes SJS and TEN, thus general causation is undisputed.

Roujeau admitted that he reported as early as 1984 that non-steroidal anti-inflammatories (NSAIDs) (including ibuprofen) were the main cause of drug-induced TEN in France. (Roujeau at 105, *App.* 12). He further reported that NSAIDs were the leading group among suspect drugs associated with SJS and TEN in a study in France (*id.* at 107, *App.* 13); and again in 1990 that NSAIDs, including ibuprofen, were associated with SJS and TEN (*id.* at 108, *App.* 13); and in 1995 in the first SCAR study report, he could not rule out a significant increase in risk of SJS and TEN associated with ibuprofen (*id.*); and finally, he admitted that in 2003 in the Mockenhaupt, *et al.*, study, his colleagues found a five-fold increase in the relative risk of SJS and TEN associated with ibuprofen that was statistically significant at the 5% level (*id.* at 108–09, *App.* 13).[4]

It should be further noted that Stern agreed that ibuprofen can cause SJS and TEN (Stern at 156–57, 164, *App.* 69, 71); that prior to the SCAR studies[5] he and most researchers in the world thought that all NSAIDs, including ibuprofen, were associated with SJS and TEN (*id.* at

[4] It should be noted that Roujeau stated that, based on an unpublished study, he had changed his mind about the causal role of SJS and TEN associated with ibuprofen; but ironically Stern disagrees with him about this, as do plaintiffs' experts. Further, this unpublished data has never been produced, so it is plaintiffs' position that it cannot be referred to in any way. In spite of this "new" data, Roujeau agreed that the "best available evidence" is the Mockenhaupt paper. (Roujeau at 113, *App.* 14).

[5] **Att. 5**—Mockenhaupt, Stern, *et al.*, The Risk of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Associated with Nonsteroidal Antiinflammatory Drugs: A Multinational Perspective, *J Rheumatol* 30:2234–40 (2003) (*App.* 147–53). An earlier study was published in 1995, Roujeau, *et al.*, Medication Use and the Risk of SJS or TEN, *N Eng J Med* 333:1600–7 (1995).

158, *App.* 70); that it was agreed that the risk of SJS and TEN was more or less of the same magnitude for all NSAIDs, including ibuprofen (*id.* at 158, 160, *App.* 70); that ibuprofen is a cause of SJS and TEN, albeit rare (*id.* at 165, *App.* 71); that "consistent observations . . . ***strongly support a causal role for some NSAIDs*** in the development of SJS and TEN"; and that "some NSAIDs" included ibuprofen (*id.*) (emphasis added).

Thus, general causation is undisputed in this case, as plaintiffs previously argued, and therefore summary judgment should be granted for plaintiffs on this issue. These admissions should also be considered against the backdrop of Wyeth's persistent failure to warn of this potentially fatal risk throughout this period.

Further, Stern's claim that the risk of SJS and TEN associated with ibuprofen is rare is belied by other published studies, and again disputed by Roujeau's testimony and the Affidavit of plaintiffs' expert, Dr. Salisbury. Roujeau admitted that *absolute* risk is the same as *excess* risk and that if Lesko, *et al.*,[6] found an absolute risk of 5.4 hospitalizations for EM[7] (which would be 54 per million users per year) this would be a significant risk, if there were an association between the adverse reaction and the drug. (Roujeau at 125–26, *App.* 15–16). Dr. Salisbury reaffirmed this excess risk and stated that it was even higher—as high as 7.2/100,000. (Salisbury Aff. at 17–19, *App.* 110–12). This is contrary to Stern's assertion in his Affidavit and report in this case that the excess risk of SJS and TEN associated with ibuprofen is "one in a million for persons that used the drug for one week." (Stern Aff. at 225[8]; *see also* discussion *infra* 26–30).

c. All known causes of TEN other than ibuprofen were excluded by the tests done.

[6] Lesko & Mitchell, An Assessment of the Safety of Pediatric Ibuprofen, *JAMA,* 273:929–33 (1995).
[7] "EM" (erythema multiforme), or "EMM" (erythema multiforme major) were all-inclusive terms that up to the late eighties and early to mid-nineties, occasionally included SJS and TEN cases as well. (Stern at 101, *App.* 60).
[8] All references to "Stern Aff." are to the *Appendix* page numbers from defendant's Summary J. Brief.

In his report in this case, defendant's expert Stern postulates that a "possible" cause of plaintiff's TEN was either herpes simplex virus (HSV), mycoplasma pneumoniae (MP), or some unknown cause, including possibly a chemical cause. (Stern Aff. at 222).[9] However, in his Affidavit filed (and apparently drafted by defense counsel), Stern beefed up his opinion, now asserting that infection or some chemical cause was the "likely cause." (Stern Aff. at 224–25).

The only possible infectious causes that were even seriously considered by the treating doctors were mycoplasma pneumoniae and herpes simplex virus. However, Roujeau admitted that "there is no clear evidence that mycoplasma caused this disease" (Labrea's TEN) (Roujeau at 44, *App.* 4); that he has studied this issue generally; and that his original research "didn't find evidence of a documented causal relationship between herpes simplex and mycoplasma pneumoniae and TEN in those studies" (*id.*, at 133–34, *App.* 17–18).

In fact, Roujeau stated categorically that there is no documented evidence in the literature of a casual connection between HSV and TEN at all (*id.* at 134, *App.* 18), nor any "documented association" of a connection between mycoplasma and TEN (*id.* at 135, *App.* 18). And indeed he could not testify based on reasonable medical probability that MP caused her TEN, with which Stern agreed. (*Id.* at 140, *App.* 19; Stern at 304–05, *App.* 89).

Moreover, Roujeau admitted that there was no evidence of any other known infectious cause, such as Klebsiella pneumonia (Roujeau at 139, *App.* 19), and no evidence of unknown viral causes in the literature, which was one of the theories floated by defendant's ID expert,

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[9] Apparently, defendant decided to drop the claim that HSV or MP was a possible or probable cause of the plaintiff's TEN, since it is not mentioned in its Brief, although it is in Stern's Affidavit, probably because all experts have admitted there is absolutely no evidence of such a connection, or of any infectious cause, for that matter. (*E.g.*, Roujeau at 44–45, 132–42, *App.* 4, 17–20). Likewise, the claim that it might have been caused by some chemical has apparently been dropped, probably because Roujeau flatly rejected it, and Stern agreed. (Stern at 171–72, *App.* 72).

Shulman, of whom they apparently did not think enough to file an affidavit from (*id.* at 143, *App.* 20). It is important to note, however, that Shulman admitted that all herpes simplex tests on the child were negative, including the tests of the blister fluid from the blisters on her cheeks, and Stern agreed with him, as did Roujeau. (**Att. 6—Dep. Dr. Shulman**, 219, *App.* 162; Stern at 303, *App.* 89; Roujeau at 190–91, *App.* 26). Finally, on his deposition, Stern agreed with Roujeau that there was no evidence of any chemical cause. (*E.g.*, Stern at 171–72, *App.* 72). Thus, all defense experts agreed that all known causes of SJS and TEN other than ibuprofen were excluded by the treating doctors, or at least there was no evidence in the test results of such causes.

C. Dr. Stern's causation opinions are based on mistaken assumptions and misstatements.

a. All experts agree that the symptoms of SJS/TEN—such as fever, malaise, sore throat, and rash—often precede the taking of NSAIDs, particularly in children.

As mentioned above, defendant's argument through Dr. Stern is a simple one: since the first symptoms of SJS/TEN occurred prior to ingesting the drug, according to their experts, the drug was not the cause. However, what this simplistic argument overlooks is that the very symptoms for which ibuprofen and other NSAIDs are given are often the same as symptoms of SJS and TEN, producing a problem known as "confounding by indication."

Stern admitted that in the 2003 Mockenhaupt paper he and his colleagues had noted that even though NSAIDs, including ibuprofen, were often given for fever and malaise that occurred before taking the drug (Stern at 174, *App.* 73), and they "had a number of cases in the SCAR study where patients had fever and malaise (two of Stern's 'compelling reasons' for concluding that ibuprofen was not the cause) prior to taking ibuprofen, [they] still found a significant increase in risk in the study as a whole between SJS and TEN and ibuprofen" (*id.* at 174–75,

App. 73).

Further, he and Roujeau both agreed that "just because the symptoms occurred before she ingested the drug does not mean that the symptoms were necessarily symptoms of SJS or TEN." (*e.g.*, Roujeau at 168, *App.* 22). Fever and sore throat, as well as rash, can be symptoms of a bacterial or viral infection, as well as symptoms of SJS and TEN. (*Id.* at 168–69, *App.* 22). Dr. Salisbury confirmed this in his Affidavit. (Salisbury Aff. at 12, *App.* 105).

Indeed, as stated above, Roujeau admitted that "just because she had bumps and a blister on her face before she took the drug does not in and of itself conclusively prove that they were symptoms of SJS and TEN" (Roujeau at 165–66, *App.* 21–22), and that "there is no good evidence" that the bumps and blisters she exhibited when she woke up were caused by SJS and TEN (*id.* at 177–78, *App.* 24–25). This admission alone should be adequate basis to grant plaintiffs' motion for summary judgment on individual causation. At the very least, it raises a material fact issue.

b. Stern was mistaken or deliberately misrepresented the facts about most of his "compelling reasons" for his opinion that ibuprofen was not the cause of her SJS and TEN.

Stern based his main opinions on the following mistaken assumptions about the facts, or misleading statements about the clinical significance of the facts, which he called "compelling reasons" for his opinions (Stern Aff. at 222, *et seq.*):

i. Stern admitted that fever prior to taking ibuprofen was normal, and not diagnostic of SJS and TEN.

The first factor that Stern lists as a "compelling reason" for concluding that ibuprofen was not the cause of her SJS and TEN was the fact that she had fever prior to taking the drug.

However, he agreed (as discussed above) that it is common for fever to precede the taking of ibuprofen, because it is one of the indications for use. (Stern at 187–88, *App.* 76). He further agreed that fever is a non-specific symptom and that "fever alone in this case is not diagnostic of SJS and TEN." (*Id.* at 189, *App.* 76). Further, he admitted that there was no evidence that she had fever until later in the day, so his assumption that she woke with fever was mistaken. (*Id.* at 190–91, *App.* 77). Thus, his implication in his Affidavit that she awoke with fever (and also malaise, as shown below) is mistaken. (Stern Aff. at 221).

ii. Stern admitted that he was mistaken about the child having awakened with "skin lesions including blistering lesions of the face."

Another "compelling reason" listed by Stern for his opinions included his erroneous conclusion that the child awoke with "blistering lesions of the face." (Stern Aff. at 223). However, he admitted that he was mistaken about this fact and that both the mother's account and the Medical City chart confirm that she only had one "blister," which was on her right cheek. (Stern at 199–200, *App.* 79).

Further, he ignored the mother's testimony that this "blister" looked more like a mosquito bite (*id.* at 201, *App.* 79); and admitted that an insect bite, such as a fire ant bite, can often turn into a blister (*id.* at 202, *App.* 80). He evaded answering whether or not these lesions were diagnostic of SJS and TEN, claiming they were "consistent . . . with the first clinical signs" of SJS and TEN, but when asked he disagreed with Dr. Roujeau that the bumps and blisters were "no good clinical or laboratory evidence" of SJS and TEN. (*Id.* at 205, *App.* 80). This disagreement between Stern and Roujeau presents the ironic situation of a material fact dispute created by a disagreement among the defendant's own expert witnesses.

Further, he acknowledged the child's previous history of skin eruptions, including dermatitis, eczema, and Tinnea Corporis (ringworm), which he agreed with Dr. Roujeau can "resemble drug eruptions" (*id.* at 172, 177, 180–81, *App.* 72, 73, 74); and he agreed that ringworm can cause vesicles or blisters and that in the SCAR study one of the signs or symptoms of SJS and TEN was vesicles, although he claimed that ringworm could only cause "micro-vesicles" (*id.* at 182–83, *App.* 75). He also admitted that the SCAR study did not exclude people solely because they had skin symptoms before taking the drug, and that the "probable index day," or date of beginning of SJS symptoms, was the "date when the first involvement of skin or mucous membranes *not explained by other conditions*" occurs. (*Id.* at 184, *App.* 75) (emphasis added).

iii. Stern also admitted that he could have been mistaken about the time interval between the development of the first mucosal lesions (the blisters on the child's lips) and the taking of ibuprofen.

In his report and Affidavit, Dr. Stern accepts as fact a statement by admitting physician Dr. Sandell that, "At that time (the time she was given Advil) the blisters began to appear on the child's lips." (Stern Aff. at 221, ¶ 3). However, the mother testified that the blisters did not appear for "an hour to two hours" after taking the Advil. **(Att. 7—Dep. LaSandra Madden**, pp. 111–12, *App.* 165).

When the blisters on her lips first appeared is very important because both Stern and Roujeau have testified that mucous membrane (mucosal) lesions are the most characteristic presentation of SJS and TEN (Roujeau at 52, *App.* 6; Stern at 121–23, *App.* 63–64); and both have admitted that the first mucosal lesions were the blisters on her lips, which if the mother is correct, occurred *after* taking the drug (Stern at 131–32, *App.* 65; Roujeau at 54, *App.* 7).

iv. Stern admitted that the clinical pattern of the child's skin lesions is almost always associated with drug-related TEN and never with herpes.

Additionally, Stern agreed that the clinical appearance of the child's initial skin lesions was characteristic of drug-induced SJS and TEN, according to a peer-reviewed journal report by Roujeau. (Stern at 109–13, *App.* 61–62). The atypical target lesions she had have been described by Roujeau as "strongly related to drugs but never to herpes."[10]

v. Stern admitted he was mistaken about the child having "generalized malaise" prior to taking ibuprofen.

Another factor listed by Stern as a "compelling reason" for his opinions about causation was that "she had generalized malaise before taking ibuprofen." (Stern Aff. at 223). However, on cross-examination he admitted he was mistaken about this fact as well. He gave the following testimony:

> Q. And I'm now asking you, again, if you can find any evidence in the chart that this child had malaise or generalized malaise when she woke up that day, or at any time that day, until much later in the day, and certainly before taking ibuprofen?
>
> A. ***No, I can't.***

(Stern at 192, *App.* 77) (emphasis added).

Even after confronted with this significant error, Stern refused to admit he was mistaken, claiming: "I may or may not be mistaken about the exact time." (*Id.* at 193, *App.* 77). When questioned further, he claimed that fever was evidence of malaise, but admitted that Dr. Sandell's Admission History at Medical City **(Att. 8—MCD chart excerpts,** p. 29, *App.* 172) stated that the child had no fever and continued to eat well all morning, which was consistent

[10] Roujeau, Erythema Multiforme With Mucous Membrane Involvement and Stevens-Johnson Syndrome are Clinical Different Disorder with Distinct Causes, *Arch Dermatol* (1995).

with the mother's testimony (Stern at 195–96, *App.* 78). Further, he admitted that even at the time the child presented to the Medical City ER there was no complaint of malaise (which he defined as lethargy), and he admitted that the ER doctor/nurse did not check "lethargic" on the Assessment Sheet, or make any reference to malaise. (*Id.* at 197, *App.* 78).

vi. Stern also misrepresented the clinical significance of "generalized itching," and was mistaken about when it occurred in relation to when she took the ibuprofen.

Another "compelling reason" given by Dr. Stern for his opinion was the alleged fact that "she had generalized itching before taking ibuprofen." (Stern Aff. at 223). However, again on cross-examination at his deposition, he admitted that he has previously written that "itching [associated with SJS and TEN lesions] is relatively uncommon." (Stern at 210, *App.* 82). Stern gave the following testimony on this issue:

> Q. My question is: Although you have told this jury that one of your compelling reasons that this child had SJS and TEN before she took ibuprofen was that she had generalized itching, you have written that generalized itching is unlikely to occur with SJS and TEN, have you not, sir?
>
> A. I have written that it is not a frequent presenting symptom.
>
> ....
>
> Q. I didn't ask you if it doesn't happen. You've written that it's unlikely to occur, have you not?
>
> A. That's what that says, yes.
>
> ***Q. That means more likely than not patients with SJS and TEN won't have itching, isn't it? Isn't that what that means?***
>
> ***A. Yes.***

(*Id.* at 213–14, *App.* 82–83) (emphasis added).

Further, he admitted that he had overlooked the mother's testimony that the itching did

not begin until a couple of hours after the child was given the Advil. (*Id.* at 217, *App.* 83).[11] Therefore, not only did he deliberately misrepresent the clinical importance of itchiness, he got the time wrong. This analysis of his "compelling reasons" shows that they are *all* either clinically insignificant or based on mistaken facts. His affidavit and opinions regarding causation are therefore essentially worthless.

vii. The timing of the SJS/TEN symptoms is consistent with ibuprofen being the cause.

Another false assertion made by Stern is that "[e]ven if . . . LaBrea Williams had used and tolerated (he did not say "reacted to") ibuprofen before, insufficient time had elapsed from her use on the afternoon of 6/1/02 to the early morning of 6/2/02 for even a previously sensitized individual to elicit the signs and symptoms described on 6/2/02." (Stern Aff. at 224, ¶ 12). Although it was initially unclear from the mother's testimony, it later became clear that the child had been given Advil in 1999 when she was hospitalized at Children's Medical Center for chicken pox. **(Att. 9—Children's Med. Ctr. records,** pp. 01–2, *App.* 186–87).

Further, Stern admitted that he had written that "Re-exposure to a causative drug is likely to lead to a more extensive and serious reaction within days *or even hours* of the re-exposure, a finding also consistent with an immunologically mediated mechanism." (Stern at 226, *App.* 85) (emphasis added). When pressed about this, he attempted to claim that this statement referred to "an individual who had displayed the Stevens-Johnson or TEN before," in other words, had a previous adverse drug reaction. (*Id.* at 227, *App.* 85) However, he admitted that nowhere in this article did he state that the prior exposure required a reaction to the drug. (*Id.*; *see also id.* at 243,

[11] The mother testified that "it was around 6:00, 6:30 that she was itchy." (LaSandra Madden at 110, *App.* 165).

App. 88). Likewise, Dr. Roujeau admitted that he had never required a prior reaction to the drug to prove sensitization. (Roujeau at 171, *App.* 23). And both defense experts agreed that prior sensitization in this child could not be excluded. (*Id.* at 173, *App.* 23; Stern at 238–40, *App.* 87).

Further, Dr. Roujeau agreed that if she had been previously sensitized to the drug a reaction to the drug could occur "very rapidly," if the individual had been sensitized to the drug *by previous use*—not by a prior reaction to the drug. (Roujeau at 173–74, *App.* 23–24). Thus, Dr. Stern's argument in his Affidavit about there not being time for the reaction to occur after taking the drug goes out the window if prior sensitization had occurred. Further, even if a prior reaction is required, which neither expert had ever required in previous writings or in their reports, Stern has written that the prior "reaction" may be as mild as a fever. (Stern at 231, *App.* 86).

viii. Dr. Roujeau admitted that the aggravation of a pre-existing viral infection by ibuprofen is known to cause serious skin reactions, and possibly SJS/TEN.

Dr. Roujeau agreed that it's well-documented in the literature that a drug can aggravate a pre-existing infection and cause a severe skin rash, and that such skin rashes are more frequent in patients with such infections. (Roujeau at 46, *App.* 5). Further, as early as 1987, he postulated that TEN could be caused by genetic predisposition plus a viral infection, plus a drug like ibuprofen. (*Id.* at 270, *App.* 28). Further, he repeated this assertion in a letter to a reputable journal in 1995. (*Id.* at 272, *App.* 28).

Further, he agreed with a statement made in an article published in 2002 in the journal *Drug Safety* by Forman, *et al.*, that: "It is biologically plausible that an interaction between an infectious agent and a drug or its metabolite may precipitate severe skin reactions." (*Id.* at 275, *App.* 29).

As shown below, this theory about the interaction between a pre-existing innocuous upper respiratory infection with ibuprofen being the cause of plaintiff's TEN (the "concurring cause" theory) is also supported by plaintiffs' expert Salisbury. This theory is supported in the literature and by defendant's own experts, and clearly explains how the pre-existing skin lesions could occur as a result of an innocuous viral infection, which when combined with the subsequent dose of Children's Advil, produced plaintiff's TEN. Neither Stern nor anyone on defendant's behalf has rebutted this theory.[12]

D. Plaintiffs' experts overwhelmingly establish individual causation.

a. Plaintiffs' experts Salisbury, Grossman, and Tackett—coupled with Stern's and Roujeau's admissions—show plaintiffs' entitlement to summary judgment on the individual causation issue.

i. Ibuprofen was a producing cause of plaintiff's TEN.

Plaintiffs have filed as summary judgment evidence the Affidavit of Dr. Roger Salisbury, a burn surgeon from White Plains, New York, who has treated approximately 400 SJS and TEN patients in his career **(Att. 4—Aff. Dr. Salisbury**, *App.* 94–118); as well as that of Dr. Moses Grossman, a distinguished expert on infectious diseases, who rules out any infectious cause, and concludes that the cause of the child's TEN was ibuprofen **(Att. 10—Aff. Dr. Grossman**, *App.* 204–11). Additionally, plaintiffs have filed the Affidavit of Dr. Randall Tackett, a pharmacologist and toxicologist, who teaches full time at the University of Georgia. **(Att. 11—Aff. Dr. Tackett**, *App.* 224–51).

These experts, fully qualified in their fields, have testified, based on a careful review of

[12] This is the exact mechanism that is postulated for the cause of Reye's Syndrome, a severe, potentially fatal viral infection that is caused by a combination of varicella (chicken pox) and other viral infections and aspirin. Thus, it is now universally known that children with viral infections shouldn't be given aspirin when they have viral infections, because of the risk of Reye's.

the medical records and literature, that ibuprofen was the cause of this child's TEN reaction. Dr. Salisbury, who is the only expert who has treated both adult and pediatric patients where TEN was caused by ibuprofen, relies on his review of the medical records in this case, his extensive review of the literature (listed in his Affidavit), and his extensive clinical experience in treating TEN patients, in concluding that ibuprofen was the cause of the child's TEN and that the defendant's failure to warn about this rare but potentially fatal skin reaction is malice as defined by Texas law. His malice opinions are contained on pp. 17–19 and 22–23 of his Affidavit (*App.* 110–12, 115–16), and are discussed *infra.*

It is Dr. Salisbury's opinion that the skin lesions the child woke up with on the morning of June 1 before ingesting ibuprofen, were a re-occurrence of her previous skin problems—as it is of Dr. Moses Grossman, plaintiffs' respected infectious disease expert—and that ibuprofen was the cause of her TEN, for the following reasons, among others, as summarized from Dr. Grossman's Affidavit:

1) Ibuprofen has been thoroughly described in the literature as being a cause of SJS and TEN.

2) Labrea had previously been exposed to ibuprofen prior to her SJS and TEN reaction on this occasion and this pattern fits with having a rapid development of her blisters after she was administered the Advil and is consistent with the scientific evidence that sensitization can occur with an initial brief exposure to the offending agent.

3) Ibuprofen has been reported to cause SJS and TEN within one to three days and within hours after as little as one dose in a sensitized individual.

4) There were no proven underlying infections that could have caused her SJS and TEN.

5) Neither herpes nor mycoplasma have been documented in this case.

6) She did not demonstrate the clinical features of an infectious process for a mycoplasma pneumoniae infection.

7) The complement fixation test for mycoplasma is not a reliable test since it has a high false positive rate affected by underlying inflammatory disease, like SJS and TEN.

8) Labrea had developed bumps from her underlying atopic dermatitis/eczema which occurred prior, during, and after her SJS reaction; therefore, the bumps that developed on her right cheek, forehead, and other cheek were not related to SJS during her SJS and TEN events in June 2002.

9) Every time ibuprofen was administered she got worse until it was stopped; then she started getting better.

(Grossman Aff. at 7, *App.* 210)

ii. Dr. Salisbury also points out that ibuprofen was probably a concurring cause if not a substantial contributing factor in plaintiff's TEN.

As noted above, defendant's whole motion is based on the supposition that unless ibuprofen was the *sole cause* of the child's TEN, plaintiffs cannot recover. However, Dr. Salisbury's Affidavit supports the proposition that even if the child had a pre-existing disease process prior to taking the ibuprofen, it could have been aggravated and contributed to by the ibuprofen. This is confirmed by Dr. Roujeau, as discussed above. Salisbury points out that, "[t]his would have occurred by an infectious process priming the immune system to react to the ibuprofen in a synergistic way to cause the SJS and TEN reaction in Labrea Williams." (Salisbury Aff. at 13, ¶ 10, *App.* 106). Defendant has offered no summary judgment evidence to rebut or refute this theory.

iii. Tackett and Salisbury have both stated that the Lymphocyte Toxicity Assay done on Labrea Williams proves conclusively that ibuprofen was the cause of

her TEN.

As shown in Plaintiffs' Motion for Partial Summary Judgment, plaintiffs have submitted the results of a laboratory test, which has been shown by reputable, peer-reviewed medical literature to be a valid measure of the cause of a previous toxic drug reaction. The results of this test are attached to plaintiffs' Motion as Att. 5, and to this Response as **Att. 12**, *App.* 328–50.[13]

As Dr. Salisbury has pointed out in his Affidavit, "[t]he positive result from the LTA, based on reasonable medical probability in conjunction with the other clinical evidence, conclusively proves that plaintiff's TEN was caused by ibuprofen by her inability to adequately detoxify ibuprofen metabolites, which set off a cytotoxic reaction caused by ibuprofen that led to her developing TEN." (Salisbury Aff. at 17, *App.* 110). This conclusion has been confirmed by Dr. Tackett in his Affidavit on pages 16–18 (*App.* 239–41), as well as by Dr. Neuman, the pharmacologist and toxicologist who ran the test. (**Att. 19—Aff. Manuela G. Neuman, Ph.D.,** pp. 6–8, *App.* 399–401).

Moreover, defendant's expert Stern has himself written favorably about this test as recently as 1996, and on his deposition he confirmed that he had written that the LTA "showed good sensitivity and specificity in Dr. Neil Shear's work." (Stern at 346–47, *App.* 90). Although he attempted to disclaim its reliability, he admitted that when asked about it on an earlier deposition he did not say it had been repudiated. (*See id.* [full exchange] at 348–53, *App.* 90–91). Further, Stern testified recently on deposition in another SJS case to the following: "The available literature for drug reactions from nonbiased series shows that for many persons who

[13] See discussion of this issue in Plaintiffs' Motion for Partial Summary Judgment with Supporting Brief, pp. 25–27, which is incorporated herein by reference.

have had adverse cutaneous reactions to a drug, they will in fact demonstrate multiple positive tests to different drugs" (referring to the LTA test). (*Id.* at 358, *App.* 93). He then attempted to claim that this was a "mistake," and he intended to change it when he signed his deposition. (*Id.* at 359–60, *App.* 93).[14]

Dr. Stern also admitted that he had testified in that case that "it (the LTA result) is a useful piece of information to make you more highly suspect that a person was reacting to a drug that had caused a previous skin reaction," but he then attempted to back out of that statement also, stating, "I apologize for my ignorance." (*Id.* at 360, *App.* 93). However, when asked for literature to back up his assertion that the test had been "repudiated," he could only cite one article, which had never previously been identified or produced, and this article does not even deal with the LTA, but rather the LTT, which is a different test.[15] (***Id.*** at 368–69, *App.* 93a).

II. DESIGN DEFECT ISSUE

A. Standard of review.

First, defendant has attempted to mislead the court by citing Tex. Civ. Prac & Rem. Code sec. 82.005, which on its face does not apply to "a drug or device, as those terms are defined in the Federal Food, Drug, and Cosmetic Act," which definition obviously includes ibuprofen. Sec. 82.005(d). The common law test for design defect presumably applies to cases that are not governed by the statute. *See Hernandez v. Tokai Corp.*, 2 S.W.3d 251, 255–67 (Tex. 1999);

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[14] However, Stern testified earlier in the deposition that he had already signed the earlier deposition (Stern at 44, *App.* 57), and then reneged on that statement as well. (*Id.* at 359, *App.* 93).

[15] This article, by Nyfeler and Pichler, was published in 1997 and does not even deal with the LTA test, but rather the Lymphocyte Transformation Test (LTT), an entirely different test. Further, in 1999 Stern wrote a chapter for Fitzpatrick, Dermatology in General Medicine, and discussed the test making no reference to his allegation that it had been repudiated, or lacked clinical utility. (*Id.* at 351–55, *App.* 91–92). There is no basis in the established medical literature for Stern's assertion that this test is not reliable or accurate.

Caterpillar, Inc. v. Shears, 911 S.W.2d 379, 384 (Tex. 1995); *Turner v. G.M. Corp.*, 584 S.W.2d 844 (Tex. 1979). The test may be the same, but the statute is inapplicable.[16]

It may be correct that determining whether a product is "unreasonably dangerous" because of a design defect under common law requires evidence of a safer design as a requisite element, *Shears*, 911 S.W.2d at 384, but defendant has not cited a single drug product liability case so holding! In fact, none of the cases defendant cites in its design defect argument deal with either prescription or over-the-counter drugs, so arguably all are inapposite.[17] However, because plaintiffs can clearly show two safer alternative designs, defendant's argument fails in any event.

B. Acetaminophen is a safer alternative design.

a. The Boston Fever Study proved that acetaminophen is a safer drug.

Defendant's claim that there is no evidence that acetaminophen is safer is false. This was shown by the Boston Fever Study, the randomized controlled clinical trial (RCT) sponsored by McNeil.[18] Clearly, defendant's own expert Shulman has admitted that: (1) He does not know of any randomized controlled trials proving that ibuprofen is safe and effective for children **(Att. 6—Shulman dep.,** pp. 127–28, *App.* 156); and (2) According to the Boston Fever Study, in a head-to-head comparison of the two drugs, ibuprofen caused GI bleeding and acetaminophen did

[16] Plaintiffs have not been able to find any drug design cases distinguishing between the standard for proving design defects in non-drugs under the statute, and the standard for drugs. However, one commentator stated in 1994 that "A plain reading of the statute makes clear to the reader that the legislature intended for manufacturers of drugs and medical devices to be exempted only from the new standard of proving safer alternative design, and not to be exempted from liability altogether. *The effect of this provision is that cases involving drugs or medical devices will have to be tried under the risk-utility standard.*" Comment, "Texas Senate Bill 4: Product Liability Legislation Analyzed," 31 Hous.L. Rev. 921, 947–48 (1994) (emphasis added).

[17] The *Danek Medical* case, decided by Judge Lindsay, cited by defendant on pg. 14 of its brief, deals with a medical device, but there are several distinctions between devices and drugs in the law, *e.g.*, in regard to federal preemption.

[18] See the discussion of the Boston Fever Study and the CAMP trial, conducted by Wyeth, at pp. 8–10 of Plaintiffs' Motion for Partial Summary Judgment, which is incorporated herein by reference.

not (*id.* at 151, *App.* 158).[19] The absolute risk of hospitalization for erythema multiforme[20] in the Boston Fever Study was 5.4/100,000 (95% CI of 1.1-16), or 54 per million, compared to an absolute risk of 3.6 for acetaminophen, and this would be the projected number of individuals in a population (who took the drug) who would have the reaction, which Shulman agreed would not be an acceptable risk (*id.* at 142–43, *App.* 157). [21]

Further, he could not deny that renal toxicity has been reported with ibuprofen, but not with acetaminophen (*id.* at 154, 156, *App.* 159); and he agreed with the American Academy of Pediatrics policy statement that "the safety and efficacy of acetaminophen in children are well-established" (*id.* at 155–56, *App.* 159); and he agreed that "there's no evidence that acetaminophen causes GI bleeding or renal toxicity in children." (*Id.* at 156, *App.* 159). Further, he agreed with a statement in an article cited on the American Academy of Pediatrics website that concludes that studies with multiple doses (of both drugs) have failed to show that one drug is better than the other; and he could not deny without doing research that both drugs are equally effective in reducing fever and pain. (*Id.* at 159–61, *App.* 160).

b. The World Health Organization found that acetaminophen (paracetamol) is equally safe and effective as ibuprofen, but rejected ibuprofen for inclusion on WHO's Essential Drugs List.

But it should also be noted that the World Health Organization (WHO), which Shulman agreed is a "respected organization" (*id.* at 168, *App.* 161), has rejected ibuprofen from its

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[19] Indeed, Shulman acknowledged that in the Boston Fever Study, the absolute risk of GI bleeding was 7.2/100,000, with zero cases of GI bleeding associated with acetaminophen; and that Wyeth considered it serious enough to add it to their OTC label for Advil in 2004. (Shulman at 151, 153–54, *App.* 158, 158–59).

[20] Which Dr. Stern testified earlier occasionally included SJS cases, *supra* at n.7.

[21] *See* Lesko & Mitchell, An Assessment of the Safety of Pediatric Ibuprofen: A Practitioner-Based Randomized Clinical Trial, *JAMA* Vol. 273, No. 12 (1995) (Att. 15 to Plaintiffs' Motion for Partial Summary Judgment), which is incorporated herein by reference.

essential drugs list, stating that "Given the efficacy and uncontroversial safety of paracetamol (with or without codeine), the use of ibuprofen *should be discouraged as an analgesic and antipyretic, in children, also for common post operative care.*" **(Att. 13—WHO doc.** [*Ex. 11 to Shulman dep. at 173–74*], *App.* 357) (emphasis added). This determination by a prestigious world health organization went on to state that "*The efficacy and safety of ibuprofen as analgesic for chronic conditions may need to be studied better before the pediatric use can be recommended.*" (*Id.*) (emphasis added).

c. The CAMP Study, conducted by Wyeth, found a significant doubling of adverse reactions overall comparing ibuprofen and acetaminophen, as well as skin reactions.

Additionally, as plaintiffs pointed out in their Motion for Partial Summary Judgment,[22] there were twice as many ADE's in the CAMP study group who received ibuprofen compared to acetaminophen; and in the Interim CAMP report, they had over twice as many skin-related ADE's associated with ibuprofen, which they deliberately diluted by adding eleven additional skin diseases that were a basis for exclusion. Finally, although Wyeth excluded all serious ADE's as unrelated to the drug, there were still 17 found by the FDA that were possibly related, including two SJS cases, which Wyeth never formally reported to the healthcare community.[23]

d. Defendant's assertion based on Stern's Affidavit that the risk of SJS/TEN associated with ibuprofen and acetaminophen are statistically the same is misleading and conclusory.

Stern makes this statement, and cites the 1995 and 2003 SCAR studies,[24] and also relies

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[22] See discussion of the CAMP study in Plaintiffs' Motion for Partial Summary Judgment, pp. 8–10, which is incorporated by reference.

[23] *See* Att. 16 to Plaintiffs' Motion for Partial Summary Judgment, deposition testimony of Dr. Sandy Furey, Wyeth Sr. Director of Medical Affairs, which is incorporated herein by reference.

[24] Stern Aff. at 225, ¶16; Roujeau, *et al.*, Medication Use and the Risk of SJS and TEN *N Eng J Med* 333:1600-7

on FDA AERS reporting data. As to the SCAR studies, neither of those studies on its face states that the risks of SJS and TEN associated with acetaminophen are statistically the same; indeed, the only statement made about acetaminophen in either study is in the 1995 study, where it is stated "For acetaminophen there were regional differences. ***No association was seen in France, with a multivariate relative risk of .6 (95 CI, 0.2to 1.3).*** In other countries there was a significantly positive association."[25] (emphasis added). None of the authors of this study have ever explained this anomalous result. Once again, Dr. Stern has expressed conclusory opinions, without stating the basis for these opinions, or providing the underlying data or calculations. These hearsay, conclusory opinions are objected to, and should be rejected for that reason alone.

Further and finally, his reliance on a comparison of the FDA AERS reports of SJS and TEN associated with ibuprofen compared with acetaminophen is laughable. Stern has stated in a previous case, "USFDA spontaneous reporting data *do not provide any useful basis for assessing the relative or absolute risk of SJS/TEN associated with various medications*."[26] (emphasis added). Yet he has offered them as evidence to this court for the fact that there's no difference in the risk of SJS and TEN between these two drugs. He obviously is willing to change his position as the need suits him, which further detracts from his credibility.

C. Dexibuprofen is also a safer alternative design.

Defendant argues—based solely on the conclusory Affidavit of Dr. William Wardell, who has spent the bulk of his career working in the pharmaceutical industry—that dexibuprofen

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(1995); Mockenhaupt, *et al.*, The Risk of SJS and TEN Associated with Nonsteroidal Anti-inflammatory Drugs: A Multinational Perspective, *J Rheum* 30:2234-40 (2003) (*App.* 147–53).

[25] Roujeau, *et al.*, p.1603 (1995).

[26] **Att. 14, Expert Report by Stern in related case** (*App.* 359–65), *Doe v. Apothecon*, with personal information about client redacted. (Stern report in *Apothecon*, p. 4, *App.* 362) (emphasis added).

is not a safer alternative design. The chemical structure of the drug and the reasons it is safer are discussed in detail by Dr. Tackett. (Tackett Aff. at 20–23, *App.* 243–46). However, defendant's assertion that Bayer's application to market it OTC was rejected because of inadequate evidence of safety is false. As stated by FDA official Dr. Hyde, the FDA stated at the outset of the hearing that "Fortunately, there is little controversy about the basic efficacy and safety study results." (Tackett Aff. at Att. 4, Tr. of NDAC hrg, p. 23, *App.* 317). Several clinical trials were conducted by Bayer, all of which showed no significant differences in safety or efficacy between racemic ibuprofen and dexibuprofen. (*Id.* at 81–84, *App.* 320–23).

Additionally, as Dr. Tackett shows, WHO data between 1996 and 2005 shows 204 cases of EM, SJS, and TEN associated with racemic ibuprofen and zero associated with dexibuprofen. (Tackett Aff. at 25, Att. 3, *App.* 248). So, if Dr. Stern is correct in his argument that more reports show a safety signal about acetaminophen, then the same is clearly true about ibuprofen compared to dexibuprofen, and this data shows *unequivocally* that dexibuprofen is safer.

Additionally, it should be pointed out that Dr. Stephen Cooper, Asst. VP for Clinical Research at Wyeth, appeared and spoke in opposition to the FDA's approval of dexibuprofen, claiming that it should not be allowed to go directly to OTC.[27] Cooper did not express any safety concerns except to speculate about whether or not dexibuprofen might cause increased GI problems, but Wyeth offered no proof of this, and none is shown by the published clinical trials.[28] Further, the FDA members pointed out during the hearing that no law requires a drug to

[27] Tackett Aff. at Att. 4, Tr. of NDAC Hrg., pp. 10–12, *App.* 314–16.

[28] Bayer presented studies involving a total of 1470 people exposed to dexibuprofen, with no serious adverse events in the dexibuprofen group, and no differences in GI problems. (***Id.*** at 67, 81–85, *App.* 319, 320–24). It should also be noted that several clinical trials have tested and approved the safety and efficacy of this drug, according to Dr. Tackett's Affidavit, p. 24 (*App.* 247), including Chlud, 1994, 1995; Klein, 1993, 1994; Kullich, et al 1994;

go Rx first—that it may go OTC unless there is evidence that it is unsafe; and certainly none was presented at this hearing. The fact that the FDA has not approved it is a factor, but Wyeth certainly should not be able to hide behind this fact when it has not sought the approval, and in fact opposed it not for safety and efficacy reasons, but rather ostensibly because it has not gone through the Rx procedure first.

III. NEGLIGENCE, BREACH OF WARRANTIES, AND DECEPTIVE TRADE ISSUES

Defendant's argument on this point is without merit. It is based on a misreading of the *Hyundai* case, which is a non-drug case based on pre-1993 law. *Hyundai Motor Co. v. Rodriguez*, 995 S.W.2d 661, 664–65 & n.14 (Tex. 1999). Further, the holding of the case is obviously limited to a situation where the plaintiff's defective design theory (there a crashworthiness case) is based on exactly the same facts as his breach of warranty claim. *See id.* at 665. This is not the case here, where the plaintiffs' defective design theory—that there was an alternative drug design that is equally effective and safer—is totally different from their failure to warn about a serious, potentially fatal skin reaction, and their negligence claims. And in *Hyundai*, the trial court submitted the negligence theory, and there was no claim on appeal that plaintiffs' negligence theory was subsumed in the products case, nor did the court hold that. *Id.*

IV. LOSS OF CONSORTIUM ISSUE

Unfortunately, defendant is correct on this issue.

V. GROSS NEGLIGENCE AND PUNITIVE DAMAGES

The essence of defendant's argument is that "plaintiff has no evidence of the objective component of gross negligence/malice." (*Defs.' Brief*, p. 21). Defendant goes on to argue that

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Mayrofer, 2001; Phelps, 2001; and Rablfs, 1996.

the reason plaintiffs' proof must fail is that "the defendant's conduct must create the 'likelihood of serious injury' to the plaintiff," and plaintiff cannot show that. This argument is patently without merit.

A. Wyeth clearly had subjective knowledge of a likelihood of serious injury to children taking Children's Advil.

To put it bluntly, this defendant is so blinded by corporate greed and arrogance, that it can't see the forest for the trees. As shown above,[29] its own expert has reported the relationship between NSAIDs and specifically ibuprofen since 1984, and in 2003 the association was confirmed to be a RR of 5.3, significant at the .05 level; yet defendant still denies this causal relationship and refuses to warn the healthcare community about it![30] As stated by Dr. Salisbury in his Affidavit, defendant has never reported any of the literature associating ibuprofen with SJS and TEN to the FDA, either in its periodic or its annual reports; nor has it warned the healthcare community or the consumer. Further, it is beyond cavil in this case that if the doctors at Medical City had been fully aware of the risk associated with ibuprofen, they would not have continued to pump this child with ibuprofen, even after she was diagnosed with SJS!

Further, also as pointed out by Salisbury, where an adverse reaction is clearly causally related to a drug, as TEN is, the issue is not whether it is rare; but rather the certainty that it will occur to at least 72/ million children, if the Boston Fever Study is believed. *When it does occur* it will be painful, disfiguring, permanently disabling, and have a high death rate. (Salisbury Aff. at 18–22, *App.* 111–15). Since it is known that there will be some cases every year, i.e., if there

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[29] *See* discussion of Dr. Roujeau's previous studies reporting an association between SJS and TEN, *supra* at 6–7.

[30] Defendant has flatly stated that it has not warned the healthcare community about the association of ibuprofen with SJS and TEN because it does not believe there is an association! **(Att. 15—Statement from latest version of Joint Status Report, pp. 6–7, 25–26,** *App.* 366–70).

is an absolute risk of as high as 72 children per million doses that may suffer serious hospitalization, this is a knowing appreciation of a high likelihood that at least 72 children or more per year will be seriously injured, and this is an unacceptable risk![31]

Further, according to Salisbury, the absolute or excess risk of SJS and TEN is much greater than reported by Dr. Stern. First of all, as noted by Dr. Salisbury, Stern's "statistics" do not accurately report the risk in the pediatric population, which Stern's own studies show is much higher.[32] Salisbury's affidavit shows that it is a high as *72 per million in children* (Salisbury Aff. at 19, *App.* 112) and, ironically, this is consistent with a study co-authored in the early nineties by Stern, where he reported the risk in the Medicaid population studied of EM/SJS was as high as *60.7 per million for children under 10*![33] This is also consistent with his 2005 study, which found that 43% of all EM/SJS/TEN hospitalizations are children under 16! *Supra* n.32. Yet Stern and Wyeth completely ignore this significantly greater risk among children in their papers and in their argument. Further, Salisbury's opinion is based on the Boston Fever Study, which as plaintiffs showed in their own Motion for Summary Judgment, was used by Wyeth as a basis for their OTC switch of Children's Advil and its approval by the FDA.

Defendant's reliance on Stern's "declaration" for the fact that the risk from all causes is

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[31] Even if the risk is only 54/million, as reported by Lesko & Mitchell in Table 3 of their report, this is an unacceptable risk, according to defendant's own expert Shulman. (Shulman at 143, *App.* 157). And as noted by Dr. Robert Nelson, plaintiffs' FDA expert, in his Affidavit in Support of Plaintiffs' Motion for Partial Summary Judgment, defendant has had 15 cases of SJS and TEN reported among children under 12 between 1993 and 2003. This Affidavit and all attachments are incorporated herein by reference. (Nelson Aff., *App.* to Pls.' Mot. For Partial Summary J., pp. 1052–53).

[32] For example, in 2005 Stern reported that 43% of all hospitalizations for EM/SJS/TEN in the United States were children under 16! [Stern, Utilization of Hospital and Outpatient Care for Adverse Cutaneous Reactions to Medications *Pharmacoepidem & Drug Safety*, (2005)].

[33] *See* Strom, Stern, *et al.*, A Population-Based Study of Stevens-Johnson Syndrome, *Arch Dermatol,* 127:831–838 (1991) (where Stern and his colleagues found a risk of EM, which at that time included cases of SJS, in children under 10 as high as *60.7 per million vs. an average of 30.4 millions for all other age groups*).

"about 2 to 5 cases occurring in a millions persons in a year" is objectionable, for several reasons, not the least of which is that it is false. First, Stern does not state the basis for this opinion, nor does he disclose his calculations. Thus, it is conclusionary to the nth degree. Nor is his conclusion that the "risk of SJS/TEN in association with ibuprofen is less than one in a million" valid summary judgment evidence for the same reason—he does not show the source of this opinion, the basis for it, or his calculations of this so-called "excess risk."

Further, as shown further by Dr. Salisbury, after a safety review of the reports of SJS and TEN coming in to them, Wyeth made a conscious decision to add SJS to its French OTC ibuprofen labeling, but not to the U.S. label! This is shown by the attached French Product Information Leaflet (PIL), which is distributed with OTC Advil in France. It is unconscionable for Wyeth to warn about this risk in France, but not in the U.S.! **(Att. 16—French label,** *App.* 371–74).[34] How could there be more evidence of a conscious and deliberate decision, in spite of the known and published risk? There is clearly evidence of a material fact issue on gross negligence and malice, and plaintiffs will prevail on this issue before the jury.

VI. CONCLUSION

Defendant's motion should be denied in all respects, except as to the loss of consortium claim. Further, plaintiffs' Motion should be granted on the failure to warn, general causation, and individual causation issues. At the very least, the Court should submit the individual causation issue to the trier of fact.

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[34] This label provides: "...In case of apparition of cutaneous or mucous signs which look like burns (redness of the skin associated to bullous, blister or ulceration) **DISCONTINUE TREATMENT AND IMMEDIATELY CONTACT A DOCTOR OR AN EMERGENCY MEDICAL SERVICE."** (emphasis in original). The warning does not mention SJS per se, but clearly describes the symptoms, and this is similar to the warning that plaintiffs are seeking in the present case.

Dated this 2nd day of June, 2005.

Respectfully submitted,

LAW OFFICES OF JAMES C. BARBER
4310 Gaston Avenue
Dallas, Texas 75246
Phone: (214) 821-8840
Fax: (214) 821-3834

By: _____
JAMES C. BARBER
State Bar No. 01706000
Pro hac vice

WATERS & KRAUS, L.L.P.

By: _____
CHARLES VALLES
State Bar No. 00789696
3219 McKinney Avenue, Suite 3000
Dallas, Texas 75204
Phone: (214) 357-6244
Fax: (214) 357-7252

ATTORNEYS FOR PLAINTIFF

CERTIFICATE OF SERVICE

This is to certify that a true and correct copy of this document has been faxed and mailed via certified mail; return receipt requested to the defendant's attorney of record in this case on this the 2nd day of June, 2005.

_____
JAMES C. BARBER